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(54) **PROCESS FO R THE PRODUCTION OF MICROSPHERES OF PANCREATIC ENZYMES WITH HIGH STABILITY**

VERFAHREN ZUR HERSTELLUNG VON PANKREASENZYM ENTHALTENDE MIKROSPHÄREN MIT HOHER STABILITÄT

PROCEDE DE FABRICATION DE MICROSPHERES D'ENZYMES PANCREATIQUES A STABILITE ELEVEE

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EP 1 335 706 B1

Description

FIELD OF THE INVENTION

[0001] The present invention refers to a process for the production of microparticles for pharmaceutical use. Microspheres including pancreatic enzymes in stabilized form are described, with high bio-availability and high enzymatic activity. The production process of said microspheres through a high-energy granulation and spheronisation process, without the presence of solvents is described.

PRIOR ART

[0002] A reduced exogenous production of enzymes by the pancreatic gland can be due to different pathologic conditions. The unsuccessful or insufficient production of digestive enzymes in particular is due to the mucoviscidosis (cystic fibrosis), to obstructions of the common bile duct, to pancreatic carcinoma and to pancreas inflammatory states (chronic pancreatitis). As a consequence the persons affected with these pathologies become unable to digest the foods by decomposing them into molecules absorbable by the gastrointestinal tract.

[0003] The disease brings to loss of weight and can have deadly outcome. The therapy consists of substitute oral administration of pancreatic enzymes of animal origin (here called "pancreatin" for the sake of brevity). The pancreatin is formed for the most part by lipase, amylase and protease; mainly the lipase catalyses the hydrolysis of the fats into fatty acids and glycerol, the amylase metabolizes the starch into dextrins and sugars and the protease decomposes the proteins into peptides and amino acids (G. J. Peschke, Pancreatic enzymes (Pancreatin), in Topics in pharmaceutical sciences, D. D. Breimer, D. J. A. Crommelin, K. K. Midha, Fédération Internationale Pharmaceutique (FIP), The Hague, 1989).

[0004] The pancreatin is extracted, preferably but not only, from the pig pancreas.

[0005] The pharmaceutical most suitable and effective form for pancreatin is that of spheres or pellets or minitablets. In case of oral administration, these formulations are provided with gastroresistant coatings: this is necessary by the fact that the pancreatic enzymes are inactivated by the acid pH of the stomach and must be delivered just when in contact with the duodenal pH.

[0006] The administration of small-sized multiparticles forms is particularly important to ensure a proper distribution of the enzymes in the food during the gastric transit and a remarkable delivery rate when the microspheres reach the duodenal pH. To improve the food digestion, it is particularly important that the microsphere are small sized, so that the enzymes are delivered onto a wide surface area and have a fast gastric transit. To this purpose Meyer has demonstrated that spheres of 1 mm passed through the stomach with times significantly shorter than spheres of 2 or 3 mm diameter (J. H. Meyer, J. Elashoff, V. Porter-Fink, J. Dressman, G. L. Amidon, Gastroenterology, 94, 1315, 1988).

[0007] Pancreatin is an enzyme with particular stability problems: it is in fact been noticed its inactivation, partial or total, in case of long exposure to water environment or heating at high temperature, or for simple storage at high temperature (G. J. Pescke, Pancreatic Enzymes (Pancreatin) ch. 10, p. 133). The most unstable among the pancreatic enzymes proves to be the lipase, which is also the most important enzyme in the substitute therapies. In tests made by the Applicant the pancreatin, preserved for 7 days at 40°C at 75% relative humidity, loses 45% to 60% of enzymatic activity (lipase).

[0008] The pancreatin lability problems have influenced all the production processes of microparticles of said enzyme, reducing the range of the micronisation processes applicable to this product.

[0009] M. Buu describes (patent TW-A-310277) the preparation of an extrudate product obtained through water granulation, desiccation, re-granulation, extrusion and following selection. JP-A-08109126 claims a production method based on the application in fluid bed of pancreatin powder on sugar spheres through the simultaneous atomisation of a water solution containing a ligant (hydroxypropylcellulose). An analogous method is described in EP-A-277741, where it is described the use of LHPC (low viscosity hydroxypropylcellulose) in water solution to apply powdered pancreatin on inert nuclei (Nonpareil seeds). All these methods involve the contact of pancreatin with water and/or other solvents in dynamic conditions of particles mixing; as also highlighted in the experimental part of the present application, the wet granulation leads to a partial denaturation of pancreatin, with the formation of granules less active than the native enzyme.

[0010] An example of preparation of pancreatin pellets without use of solvents is described by Faassen and Vromans in WO-A-9638169: pancreatin is compressed by means of a roll compactor and then shelled to obtain irregularly-shaped pellets. DE 199 07 764 discloses coated pancreatin granules, i.e. irregularly shaped particles deriving from pancreatin raw particles. Boedecker et al. have obtained regularly-shaped pellets through extrusion and following spheronisation: in their EP-A-583726 is described the production of pellets with sizes included between 0.7 and 1.4 mm. An extrusion process is used also in the patent JP-A-04187085, to obtain pellets with sizes 1.5 to 3 mm; as extrusion solvent is used water or a mixture of water and ethyl alcohol. Atzl et al. (WO-A-9107948) use a process similar to wet

granulation to obtain spherical particles with sizes 0.3 to 4 mm. In DE-A-A3422619 minitablets are obtained with diameter of 1-2.5 mm and height 1-2.5 mm through compression with suitably modified punches. In DE-A-2923279, assigned to Fischer et al., pancreatin is extruded in presence of isopropyl alcohol or acetone, spheronized and finally desiccated. The above mentioned extrusion processes give irregular surface particles which require further size homogenization processes, with consequent longer production time and greater enzyme inactivation risk. This goes to the detriment of the enzyme stability and involves high industrial costs; moreover, as proved in the experimental part, the extrusion processes in presence of solvent, presents serious problems of loss of enzymatic activity. In the light of the prior art, it lacks an efficient process, having an industrial low cost, giving a very fine pellet size without causing denaturation and loss of enzymatic activity; moreover are not yet available pancreatin microspheres with reduced size and high enzymatic activity.

SUMMARY

[0011] The present invention refers to a process to obtain new microspheres including pancreatic enzymes. The process here described does not involve the use of solvents and proves to be remarkably shorter and efficient than the prior art methods. The obtained microspheres, including one or more pancreatic enzymes, one or more hydrophilic low-melting polymers and eventual excipients, have a high enzymatic activity, bio-availability and stability.

FIGURES DESCRIPTION

[0012] Figures 1A and 1B: Course of the enzymatic title (lipase) of microsphere produced according to the present invention, during 6 months period.

DETAILED DESCRIPTION OF THE INVENTION

[0013] Object of the present invention is a process allowing to obtain microspheres of pancreatic enzymes having extremely reduced sizes and a high and stable enzymatic activity.

[0014] The process is characterized in that a solid mixture including one or more pancreatic enzymes, one or more hydrophilic low-melting polymers and eventual excipients, is heated at a temperature equal or higher than the melting temperature of said hydrophilic low-melting polymer, under stirring.

[0015] The components of the mixture to be used in the process are described in detail as follows.

[0016] With "pancreatic enzymes" is meant any one of the enzymes included in the pancreatic secretion, such as amylase, lipase, protease, or their mixture in any proportion, or any extract of pancreatic origin having enzymatic activity, such as pancreatin.

[0017] Said enzymes can be indifferently obtained through extractive way from the pancreas, or produced artificially, for example through synthetic or recombinant way; in the present process they are preferably used in form of powder.

[0018] The hydrophilic low-melting polymer has melting point between 20°C and 90°C, preferably between 30°C and 70°C. Examples of hydrophilic low-melting polymers are: polyethylene glycol (Lutrol E®, Sentry® Carbonwax®), polyoxyethylene (Sentry® Polyox® WSR), copolymers of polyoxyethylene-polyoxypropylene (Lutrol F®). The spheronisation mixture can include as well other excipients normally used in the pharmaceutical art, for example lubricants, glidants, coloring agents, diluents. Among these last ones it can be mentioned lactose (anhydrous or hydrate), microcrystalline cellulose (Avicel®, Emcocel®), calcium phosphate (Di Cafos®). In general, all the excipients which could improve or make more efficient the spheronisation can be added to the composition

[0019] The composition of the mixture subjected to the process object of the invention includes: pancreatic enzyme/s, in weight rate between 40% and 99%, preferably between 60% and 85%, and hydrophilic polymer/s, between 1% and 60%, preferably between 15% and 40%.

[0020] The ratio between enzyme and hydrophilic low-melting polymer in the starting mixture is preferably between 4:1 and 1:1.

[0021] In the process object of the invention, the above described mixture is aggregated in micropellets and the micropellets are simultaneously subjected to a spheronisation process which regularise their surface. The process in question includes, in particular, the following stages:

a: loading of a suitable reactor with said solid mixture or with its single components in solid state;
b: stirring of the mixture under high-energy condition and heating of the mixture at a temperature equal or higher than the melting temperature of said hydrophilic polymer;
c: cooling of the mixture under stirring condition;
d: recovery of the solidified microspheres.

[0022] In case the mixture includes more hydrophilic low-melting polymers, the mixture is heated at a temperature corresponding or higher than the melting temperature of the polymer with the highest melting point.

[0023] A fundamental feature to obtain the microspheres with the here described properties is to avoid the direct adding of any liquid to the solid mass. The process is then carried out in total absence of solvents, both watery or organic, and avoiding any adding to the solid mass of polymers in melted state; it is then critical that all the mixture components are introduced into the reactor in the solid state before any heating is started.

[0024] The process is advantageously performed in a granulator-mixer or fluid bed. Devices preferred for the performing of the process are the high-energy granulator-mixers, such as for example Zanchetta Roto, Diosna P, Niro Pellmix, Henschel, Robot Coupe RSI, Glatt VG, or the fluid beds provided with rotating disc such as for example the Glatt ones with Rotor insertion, the Aeromatic ones provided with rotating disc, the ICO PaG ones with insertion "tangential spray" and the Victor one series FL "rotary disc".

[0025] All these devices have in common that the mixture is subjected to a high-energy mixing action and is simultaneously heated at a temperature higher or equal to the melting one of the used hydrophilic polymer.

[0026] The stirring and heating action is performed for a total time (for instance 30'-75') sufficient to obtain the desired spheronisation degree. The temperature is then lowered to allow the microspheres to solidify; the mixing goes on, possibly with less energy, during the solidification stage (for instance for 10'-50'); the process ends with the interruption of the mixing and the recovery of the microspheres. The whole process normally takes between 15' and 150', preferably between 50' and 100'.

[0027] The microspheres can be sieved through a vibrating sieve to reject eventual particles out of the required size standards.

[0028] The so obtained microspheres, in particular the ones destined to the oral administration, are advantageously provided with a gastroresistant coating, (preferably non soluble at pH lower than 5.5), such to ensure the delivery of the active principle just when the duodenum is reached, this way protecting it from the gastric pH; the application of said coating polymers is performed through spraying according to the prior art, in a fluid bed or in a spraying pan: coating is easy because of the spherical and regular surface of the microspheres. Examples of gastroresistant polymers which can be applied are: hydroxypropylmethylcellulose phthalate (for instance HP-50 or HP-55), hydroxypropylmethylcellulose acetate succinate (Aqoat®), acrylates (for instance Eudragit® L30D) polyvinylacetophthalate (Sureteric®). To improve the applicability and the stability of the polymeric membranes formed by these polymers it can be added, mixed to the same coating, plasticizing agents such as for instance, triethylcitrate or dibutylphthalate. Moreover the gliding agents like the talc are helpful to reduce the adhesion among the pellets during the coating process.

[0029] The hydrophily of the above mentioned hydrophilic low-melting polymers allow the microspheres of the invention to quickly get the enzymes bio-available in the duodenal environment, once the gastroresistan coating is dissolved.

[0030] The microspheres of pancreatic enzymes obtained according to the present invention have high bio-availability.

[0031] The present process allows in fact to obtain new microspheres of pancreatic enzymes, having the following features: (a) reduced size, with diameter between 10 μm and 1500 μm, Preferably between 100 μm and 800 μm, thus with a high bio-availability of the enzyme once administered; (b) high enzyme title; with high enzymatic title is meant an enzymatic title of the microsphere (measured in unit FIP/mg) equal to or higher than 90%, preferably equal to or higher than 95%, than the title of the solid mixture (enzyme, hydrophilic polymer and excipients in their initial quantities) from which they were produced; said mixture is in the following indicated as "physical mixture of their components". In other words, the activity of the pancreatic enzyme contained in the present microspheres is ≥ 90%, preferably ≥ 95% of the activity of the native, untreated enzyme.

[0032] In case the microspheres include more than one pancreatic enzyme, the above mentioned enzymatic title is to be determined with reference to the activity of the most thermolabile among them; for instance, in the case of pancreatin (which includes lipase, amylase and protease), the enzyme whose title is measured is lipase.

[0033] The microspheres obtained according to the present invention have a high surface regularity and a prolonged stability of the enzymatic title in time.

[0034] The microspheres obtained according the present invention includes one or more pancreatic enzymes, in weight ratio between 40% and 99%, preferably between 60% and 85%; one or more hydrophilic polymers, in quantity from 1% to 60%, preferably between 15% and 40%, and excipients pharmaceutically acceptable.

[0035] Further described are pharmaceutical compositions including the above described microspheres (eventually coated with coating polymers) and other excipients suitable for the pharmaceutical use, for example lubricants, gliding agents, coloring agents, diluents, etc. Said compositions can be formulated in forms suitable for the human or animal administration, for instance powders or pellets in sachets to dilute into water when used, suspensions, capsules of hard or soft gelatine, tablets or microtablets.

[0036] The present invention offers several advantages: the direct spheronisation process is quick and inexpensive, since it is not necessary to use organic solvents, expensive and potentially dangerous if wasted in the environment,

nor water, which requires long desiccation times and could inactivate the enzymes. Contrary to all expectations, this process can be efficiently performed even at temperatures higher than the ones of said enzymes denaturation, without reducing the activity in the latter. The so produced microspheres have a very reduced diameter, lower than 700 μm on average, thus allowing a high bio-availability. The microspheres' regular surface allows to obtain pharmaceutical coated forms using a smaller quantity of coating polymers: this allows to reduce the quantity of coating agent and the time required for the coating, so reducing the process costs and the enzyme inactivation risks. As highlighted in the experimental part, the microspheres have an enzymatic title substantially unchanged as the native enzyme and a high activity persistence in storage condition, so allowing the production of pharmaceutical compositions of pancreatic enzymes with high activity and stability.

[0037] The present invention is now described through the following not limitative examples.

EXPERIMENTAL PART

[0038] The production techniques of microspheres including pancreatic enzymes used as comparison with the present invention are: application of pancreatin on inert nucleus seed(ex. 1); extrusion and spheronisation (ex. 2). The process according to the present invention (direct spheronisation) is performed in a fluid bed with rotating disc (ex. 3), or with high-energy granulator-mixer (ex. 4). The enzymatic activity is measured as lipasic activity: this enzyme has been chosen as reference since it is the most labile among the pancreatic enzymes. The activity is determined according to analytical assays of biological type described in the European and American Pharmacopoeia and are expressed in Unit/mg (Unit FIP or Unit USP according to the used assay). According to the European Pharmacopoeia 1 mg of pancreatin has to contain not less than 1 U-FIP of proteolitic activity, not less than 15 U-FIP of lipolitic activity and not less than 12 U-FIP of amilolitic activity.

Example 1 (Reference)

Preparation of pancreatin pellets through powder application on inert nuclei

[0039] In the basket of a fluid bed of the type Glatt GPCG-1 provided with rotor insertion (rotating disc) are placed 798.0 g of neutral pellets (type "non-pareil seeds", formed by saccharose and maize starch) having sizes between 250 and 350 μm. The pellets are heated to 23°C by blowing warm air at 28°C. The entering air speed is 1 m/sec for the process whole time. Separately the powdered pancreatin is mixed with 2.0% by weight of colloidal silica (Aerosil® V200) to improve its flowability. The entering air temperature in the fluid bed is increased to 54°C so that the pellets temperature is about 27-28°C, and 490.0 g of said mixture are applied through a proportioning device Heton Feeder at a rate of 26 g/min, while simultaneously demineralized water is sprayed through a nozzle with a 0.8 mm hole and a flow rate of about 5-6 g/min. The filtering hoses are shaken for 5 seconds any 12 sec at the beginning of the process. After 25 minutes application it is necessary to shake the hoses for 5 sec any 6 sec. The pellets are dessicated by blowing air at 50°C, so to remove traces of residual water, and finally cooled by 30°C air for 10 minutes. The total time of the process is 120 minutes. This technique involves long process times since large amounts of active principle are brought into the filtering hoses by the air stream; the size of the microspheres is difficult to control. The theoretical title of the pellets (lipase), calculated by the composition, was 18.27 U-USP/mg. The obtained lipase title was, on the contrary, 8.39 U-USP/mg. This technique involves a loss in the enzymatic activity equal to 54%.

Example 2 (Reference)

Preparation of pancreatin pellets through extrusion-spheronisation

[0040] 660.0 g of pancreatin, 2465.1 g of Avicel® PH101 (microcrystalline cellulose), 165.0 g of Kollidon® K30 (polyvinylpyrrolidone) and 9.9 g of Syloid® 244 (colloidal silica) are mixed in an 18 liters mixing cube at 18 rpm for 15 minutes. The mixture is fed through a co-rotating double screw extruder TSA EF 26-20. The cochlea of the feeding hopper is in position III, while the extruder cochlea is rotated at 125 rpm. Simultaneously a solution is fed including demineralized water and isopropyl alcohol in proportion 4:1 w/w by means of a peristaltic pump Watson-Marlow at about 20 g/min. The product is extruded with a 0.4 mm axial die. The total extrusion time is 102 minutes. Immediately after the extrusion, the product is spheronized with a spheronizer Glatt P-50 with rotating speed of 750 rpm for 3 minutes. The so obtained pellets are desiccated in thermostatic furnace at 35 °C for 15 hours. The theoretical title of the pellets, calculated by the composition, was 16.25 U-FIP/mg. The obtained lipase title was, on the contrary, 0 U-FIP /mg. It is supposed that the lipase is degraded (100% activity loss) because of the process conditions (overheating of the product and/or presence of water in the extruded mass).

[0041] Further reference experiments made by the Applicant, did not highlight any better results: the wet granulation

produces pellets with irregular surface requiring too high quantity of gastroresistant coating polymers; the application of pancreatin on pancreatin pellets (in fluid bed with rotating disc Glatt GPCG-1 with insertion Rotor "tangential spray") is a too long process, with frequent stoppage of the filter hoses, and with difficulty in controlling the microspheres sizes.

Example 3

Preparation of Aancreatin pellets through direct spheronisation in fluid bed

[0042] 680.0 g of pancreatin and 320.0 g of PEG400 (polyethylene glycol) are placed in the basket of a fluid bed Glatt GPCG-1 provided with Rotor insertion. The disc is of the knurled type and revolves at 1200 rpm, while simultaneously air is blown at 70°C at about 1-2 m/sec. The filter hoses are shaken for 5 sec any 6 sec. After 60 minutes spheronisation the entering air temperature is lowered to 20°C to obtain the hardening of the pellets, while the disc rotation keeps on at 700 rpm. In this stage the shaking of the filters is of 5 sec any 12 sec. After about 30 min cooling the product is unloaded from the basket of the fluid bed. The process total time is 90 minutes. The theoretical title of the pellets, calculated by the composition, was 40.12 U-FIP/mg. The obtained enzymatic title (lipase) was 38.12 U-FIP/mg, with an activity loss lower than 5%.

[0043] In all test the ponderal yield of pellets having sizes between 150 μm and 700 μm was measured (Table 1). With the same percentual compositions, by increasing the disc rotation speed, it was possible to reduce the spheronisation time, whereas the diameter of the microspheres did not change remarkably (Table 2).

Example 4

Preparation of pancreatin pellets through direct spheronisation in mixer-granulator

[0044] 717.8 g of pancreatin and 190.8 of PEG4000 (polyethylene glycol) are placed in the tank of an high-energy mixer-granulator Zanchetta Rotolab. The blades of the machine are run at 900 rpm and the heating jacket is set at 75°C. After 45 minutes spheronisation the heating is switched off, the blades speed is lowered to 120 rpm and the jacket is cooled through pipe water flow. After 15 minutes cooling the pellets are unloaded. The process total time is 60 minutes. The theoretical title of the pellets, calculated by the composition, was 65.87 U-FIP/mg. The obtained enzymatic title (lipase) was 67.80 U-FIP/mg.

[0045] Using the described process, with a mixer-granulator Zanchetta Rotolab P-50 spherical pellets are obtained which are afterwards coated with a gastroresistant membrane formed by HP-55, triethylcitrate and talc. The coated pellets are wrapped up in thermo-sealed sachets (formed by a triple layer of paper, aluminum and polyethylene) and subjected to stability test at 25°C + 60% UR and at 30°C + 60% UR. The stability results of two lots made according to this process, expressed in percentage residual lipase activity, are reported in Figure 1: it is to notice that the microsphere enzymatic activity remains substantially unchanged (fluctuating in a range of 90-110% of the initial value) during the whole test time (6 months).

[0046] In short, the data of the above reported examples show that, while the known processes (reference examples 1-2) bring to a substantial reduction in the enzymatic activity, the process object of the present invention (examples 3-4) allows to obtain microspheres having very small sizes (<700 μm) and an enzymatic title 95% to over 100% than the native enzyme, thus substantially unchanged; the stability in time of these values is confirmed by the data in figure 1. Said results then highlight the unforeseen efficiency of the process of the present invention and the better performance of the microspheres so obtained. Further tests have been made in the condition of the example 3, changing the hydrophilic low-melting polymer concentration and the disc rotation speed. The table 1 and 2 show the process yield. The PEG concentration is measured as weight rate of PEG with respect to the starting mixture; the process yield is calculated as weight rate (with respect to the starting mixture) of the microspheres fraction having dimensions included between 150 and 700 μm.

Table 1.

PEG(%)	ROTATION SPEED (RPM)	PROCESS YIELD (WEIGHT % 150-700μM)
20	700	48.9
25	700	58.1
30	700	80.6
32	700	91.8

[0047] Increasing the disc rotation speed to 1200 rpm (table 2) the yield values are not remarkably changed, while it has proved possible to reduce of 10-15% the process total time, to advantage of the enzyme stability.

Table 2.

PEG(%)	ROTATION SPEED (RPM)	PROCESS YIELD (WEIGHT % 150-700μM)
20	1200	41.6
25	1200	47.9
30	1200	83.3
32	1200	90.8

Claims

1. A process for the production of microspheres containing one or more pancreatic enzymes, one or more hydrophilic low melting polymers, and optionally excipients for pharmaceutical use, said microspheres having diameter comprised between 10 μm and 1500 μm and enzymatic title equal to or higher than 90% of the title of the solid mixture of their components, **characterized in that** a solid mixture formed by one or more pancreatic enzymes, one or more hydrophilic low melting polymers and optional excipients, is heated to a temperature equal to or higher than the melting temperature of said hydrophilic low melting polymer, in stirring condition.

2. A process according to claim 1, including the following stages:

   a. loading of a suitable reactor with said solid mixture or its single components in solid state;
   b: stirring of the mixture at high-energy conditions and heating of the mixture at a temperature equal to or higher than the melting temperature of said hydrophilic polymer;
   c: cooling of the mixture while stirring;
   d: recovery of the solidified microspheres.

3. A process according to claims 1-2, where said hydrophilic polymer has a melting point between 20°C and 90°C.

4. A process according to claims 1-3, where said hydrophilic polymer has a melting point between 30°C and 70°C.

5. A process according to claims 1-4, where said solid mixture includes, besides optional excipients from 15% to 40% w/w of said hydrophilic polymer and from 60% to 85% w/w of said pancreatic enzymes.

6. A process according to claims 1-5, where said hydrophilic polymer is chosen among polyethylene glycol, polyoxyethylene, copolymers of polyoxethylene and polyoxypropylene or mixtures thereof.

7. A process according to claims 1-6, performed within an high-energy mixer-granulator or in a fluid bed with rotating disc.

8. A process according to claims 1-7, where the obtained microspheres are further coated with a polymeric film.

Patentansprüche

1. Ein Verfahren zur Herstellung von Mikrokügelchen (Mikrosphären) enthaltend ein Pankreasenzym oder mehrere Pankreasenzyme, ein hydrophiles bei niedriger Temperatur schmelzendes Polymer oder mehrere dieser Polymere und optional Trägersubstanzen zur pharmazeutischen Verwendung. Genannte Mikrokügelchen haben einen Durchmesser von 10 μm bis 1500 μm und einen enzymatischen Titel, der gleich oder höher liegt als 90% des Titels der Festmischung ihrer Komponenten, **dadurch gekennzeichnet, dass** eine Festmischung, welche aus einem Pankreasenzym oder mehreren Pankreasenzymen, einem hydrophilen bei niedriger Temperatur schmelzenden Polymer oder mehreren dieser Polymere und optional Trägersubstanzen besteht, unter Rühren auf eine Temperatur gebracht wird, die gleich der Schmelztemperatur des genannten hydrophilen bei niedriger Temperatur schmelzenden Polymers ist oder darüber liegt.

2. Verfahren gemäß Anspruch 1, die folgenden Schritte umfassend:

a: Beladung eines geeigneten Reaktors mit genannter Festmischung oder den einzelnen Komponenten in festem Zustand;
b: Rühren der Mischung unter hoch energetischen Bedingungen und Erhitzen der Mischung auf eine Temperatur, die gleich der Schmelztemperatur des genannten Polymer ist oder höher;
c: Abkühlen der Mischung unter Rühren;
d: Gewinnung der verfestigten Mikrokügelchen.

3. Ein Verfahren gemäß den Ansprüchen 1-2, wobei das genannte hydrophile Polymer einen Schmelzpunkt zwischen 20°C und 90°C besitzt.

4. Ein Verfahren gemäß den Ansprüchen 1-3, wobei das genannte hydrophile Polymer einen Schmelzpunkt zwischen 30°C und 70°C besitzt.

5. Ein Verfahren gemäß den Ansprüchen 1-4, wobei die genannte Festmischung neben den optionalen Trägersubstanzen 15% bis 40% w/w an genanntem hydrophilen Polymer und 60% bis 85% w/w an genannten Pankreasenzymen enthält.

6. Ein Verfahren gemäß den Ansprüchen 1-5, wobei das genannte hydrophile Polymer ausgewählt wird unter Polyethylenglycol, Polyoxyethylen, Copolymeren von Polyoxyethylen und Polyoxypropylen oder Mischungen daraus.

7. Ein Verfahren gemäß den Ansprüchen 1-6 durchgeführt mit einem hoch energetischen Mixer-Granulator oder in einem Flüssigbett mit rotierenden Scheiben.

8. Ein Verfahren gemäß den Ansprüchen 1-7, wobei die erhaltenen Mikrokügelchen im Weiteren mit einem Polymerfilm überzogen werden.

Revendications

1. Procédé pour la production de microsphères contenant une ou plusieurs enzymes pancréatiques, un ou plusieurs polymères hydrophiles à faible point de fusion et facultativement des excipients pour usage pharmaceutique, lesdites microsphères ayant un diamètre compris entre 10 µm et 1500 µm et un titre enzymatique égal à ou plus élevé que 90% du titre du mélange solide de leurs composants, **caractérisé en ce qu'**un mélange solide formé par une ou plusieurs enzymes pancréatiques, un ou plusieurs polymères hydrophiles à faible point de fusion et des excipients facultatifs est chauffé à une température égale à ou plus élevée que la température de fusion dudit polymère hydrophile à faible point de fusion, en condition d'agitation.

2. Procédé selon la revendication 1, comprenant les étapes suivantes:

a) chargement d'un réacteur approprié dudit mélange solide ou de ses composants individuels à l'état solide;
b) agitation du mélange en conditions de forte énergie et chauffage du mélange à une température égale à ou plus élevée que la température de fusion dudit polymère hydrophile;
c) refroidissement du mélange tout en agitant;
d) récupération des microsphères solidifiées.

3. Procédé selon les revendications 1-2, où ledit polymère hydrophile a un point de fusion compris entre 20°C et 90°C.

4. Procédé selon les revendications 1-3 où ledit polymère hydrophile a un point de fusion compris entre 30°C et 70°C.

5. Procédé selon les revendications 1-4, où ledit mélange solide comprend, outre des excipients facultatifs, de 15% à 40% p/p dudit polymère hydrophile et de 60% à 85% p/p desdites enzymes pancréatiques.

6. Procédé selon les revendications 1-5 où ledit polymère hydrophile est choisi parmi polyéthylène glycol, polyoxyéthylène, copolymères de polyoxyéthylène et polyoxypropylène ou leurs mélanges.

7. Procédé selon les revendications 1-6 accompli avec un granulateur-mélangeur de forte énergie ou dans un lit

fluide avec un disque rotatif.

8. Procédé selon les revendications 1-7 où les microsphères obtenues sont encore enrobées d'un film polymérique.

Fig. 1A

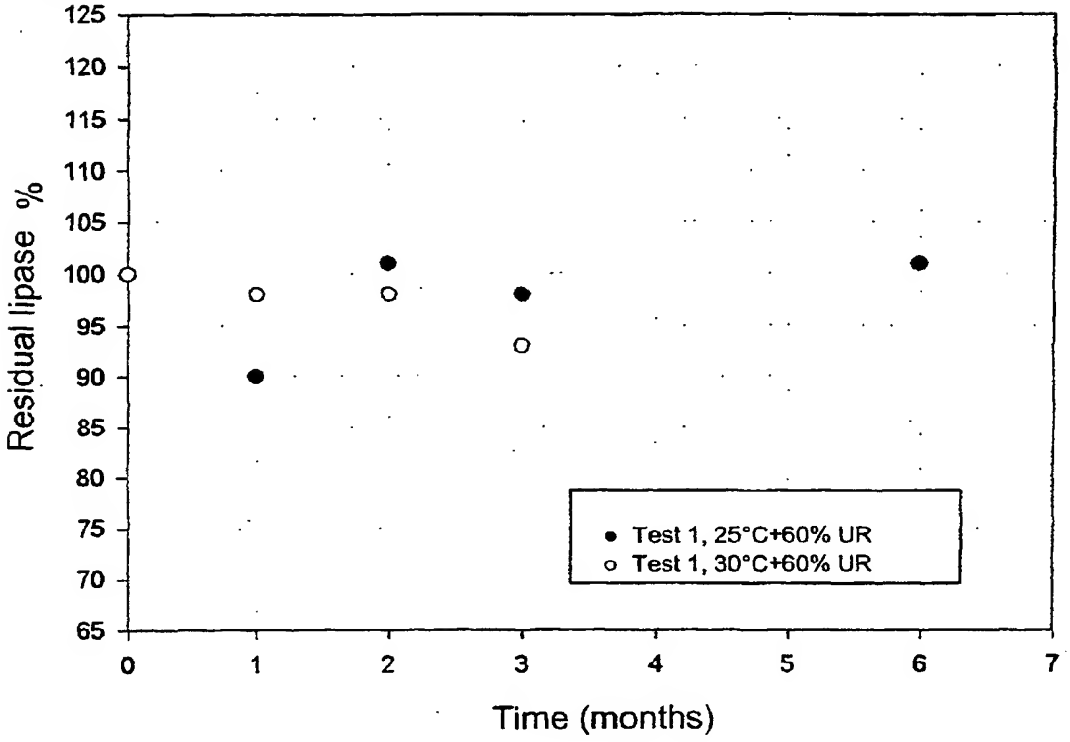
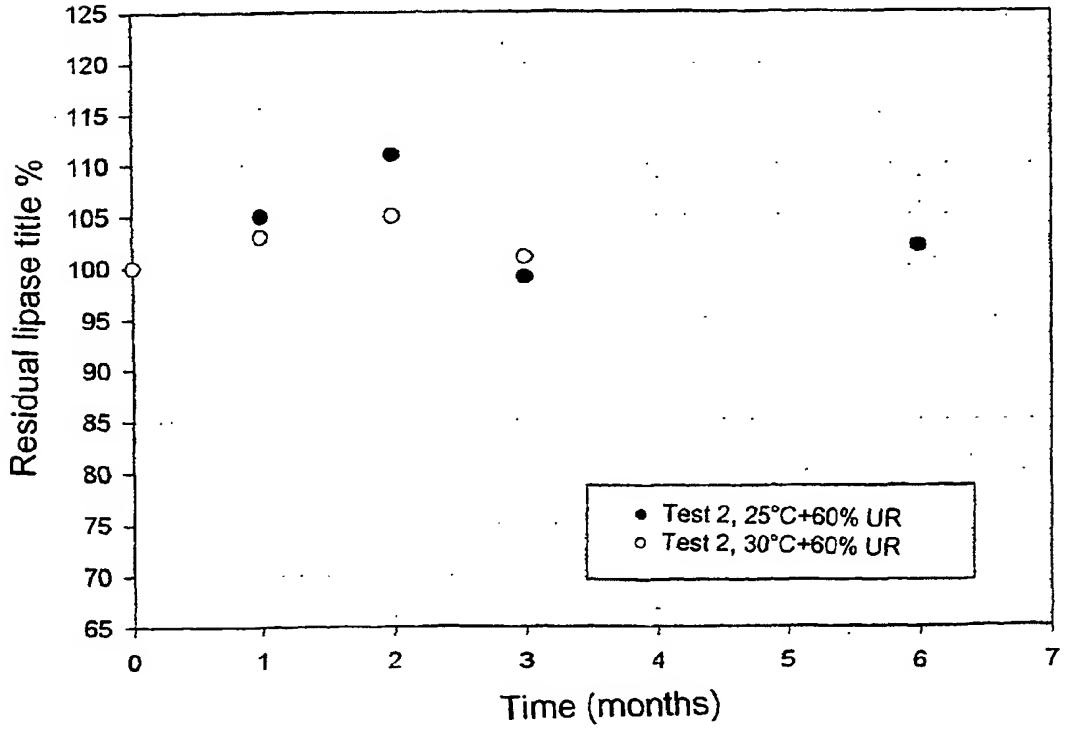

Residual lipase %
125
120
115
110
105
100
95
90
85
80
75
70
65
0
1
2
3
4
5
6
7
Time (months)
Test 1, 25°C+60% UR
Test 1, 30°C+60% UR

Fig. 1B


Residual lipase title %
125
120
115
110
105
100
95
90
85
80
75
70
65
0
1
2
3
4
5
6
7
Time (months)
Test 2, 25°C+60% UR
Test 2, 30°C+60% UR